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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,113	03/10/2004	Myron Spector	1194-176	2494

6449 7590 10/07/2010

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EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
10/07/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/796,113	SPECTOR ET AL.	
	Examiner	Art Unit	
	STEPHEN GUCKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-7,9-11,14-17,19 and 22-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-7,9-11,14-17,19 and 22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/5/10 has been entered.

2. Applicant's response filed 8/5/10 has not obviated any previous grounds of rejection. All rejections of record are maintained.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 2-3, 5-6, 9-11, 19, 14-16, 22-30, and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (reference 19 of IDS filed 3/10/04, "Chamberlain") in view of Geistlich et al. (reference 5 of IDS filed 3/10/04, US 5,837,278, "'278

patent") and further in view of Geistlich et al. (reference 1 of IDS filed 3/10/04, US 6,221,109, "'109 patent") for reasons of record and the following. Chamberlain teaches collagen tubes for nerve regeneration that can be filled with a type I collagen/chondroitin-6-sulfate material (collagen and a glycosaminoglycan copolymer known as collagen-GAG (CG) copolymer) that acts as a nerve growth stimulant, and said tube is 20mm long with an internal diameter of 1.5mm (abstract, pages 1394-1395, and Figure 1). The collagen fiber filling material is longitudinally oriented with respect to the tube (page 1395). Laminin can be a promoter of nerve regeneration inside the tube (page 1394). Chamberlain discloses methods of placing nerves inside the tubes for regeneration (abstract and pages 1395-1396). (Myron Spector is a co-author of the Chamberlain et al. reference, and is also a co-inventor of the instant Application). Chamberlain does not teach a tube formed from a single sheet of collagen prepared from peritoneal membrane that has an outer smooth barrier surface and a soft fibrous surface opposite the smooth barrier surface. The '278 patent discloses a single sheet of a resorbable sidewall material consisting essentially of a single layer collagen sheet material having a compact, smooth outer barrier surface so as to inhibit cell adhesion thereon and act as a barrier to prevent passage of cells there through, and this sheet material further has a fibrous inner surface opposite the smooth barrier surface (column 1, line 51 to column 2, line 6) derived from collagen membrane peritoneal tissue (column 2, lines 52-60). This single layer collagen sheet material is identified as Bio-Gide® by the instant specification (page 3, paragraphs 0017 and 0018), and is the same material disclosed in the '278 patent. Bio-Gide® inherently meets all the claim limitations of claims 2-3, 11, 14-15, 23-28, and 33. (Peter Geistlich is a co-inventor for the '278 patent and is a co-inventor of the instant Application).

The '278 patent does not disclose that Bio-Gide® is suitable for use with nerve tissue. The '109 patent (second Geistlich et al. reference) teaches that Bio-Gide® can be wrapped around the spinal cord and dura sheath in order to protect both from injury during spinal surgeries and also to protect the spinal area from ingrowth of connective tissue and undesired cells which might interfere with proper healing (column 1, lines 9-18 and column 1, line 54 to column 2, line 9. Also see Figures 1 and 3). It would have been obvious to one of ordinary skill in the art at the time of the invention to make and use the collagen tubes of Chamberlain with the Bio-Gide® of the prior art patents because while Chamberlain teaches that collagen tubes have multiple advantages over silicone tubes, "the required characteristics of a nerve guide remain to be fully delineated" (page 1401). While porous collagen tubes permit diffusion of nutrients and growth-promoting factors from the external environment to the injured nerves in order to promote nerve regeneration (an observation supported by two studies according to Chamberlain), if the tube is too porous, important wound-derived neurotrophic factors may be allowed to exit the injury site prematurely through the tube. Chamberlain reports that his own study has shown that the most favourable results were obtained with a non-porous collagen tube filled with a CG copolymer because said tube facilitated the retention of the endogenous neurotrophic factors in the nerve injury gap site while allowing for the infiltration of smaller molecular weight nutrients through the tube. Chamberlain concludes "additional experimentation with porous and non-porous collagen tubes that differ in permeability may be used to address this issue" (page 1402), which is an explicit direct suggestion by the primary reference to substitute the finite group of other known collagen tubes for the known and motivating purpose of improving the therapeutic results. A clear nexus thus forms between the

‘109 patent which teaches Bio-Gide® collagen membranes formed into a tube around nerve tissue (spinal cord) (Figure 1 of the ‘109 patent) with the smooth barrier face facing the exterior to protect the surgical site from ingrowth of unwanted cells (column 3, lines 5-10) while the fibrous face opposite the smooth face faces inward, allowing cell growth thereon (column 2, lines 1-4 and Figure 3), and the Chamberlain reference which discloses that “in the tubulization method of treating nerve gaps, tubes can enhance regeneration by serving to (1) contain matrices that have been found to enhance the regenerative process, perhaps by providing a scaffold for ‘contact guidance'...(2) prevent ingrowth of adjacent tissue into the gap, and thereby prevent fibrocollagenous scar formation in the gap" (pages 1399-1400). Both the '109 patent and Chamberlain share a nexus to combine Bio-Gide® with the nerve regeneration methods of Chamberlain because Bio-Gide® has an interior surface that allows cell growth thereon (‘109 patent) which is very similar to providing a scaffold for ‘contact guidance’ (Chamberlain). Likewise, Bio-Gide® has an exterior surface preventing ingrowth of unwanted cells (‘109 patent) which is exactly equivalent to preventing ingrowth of tissue that would form scars in the nerve gap and inhibit nerve regeneration (Chamberlain). The ‘278 patent makes the connection between Chamberlain’s suggestion to try other collagen tube materials in order to make and use a better nerve regeneration tube with the Bio-Gide® of the ‘109 patent even stronger because the ‘278 patent reiterates the advantages of Bio-Gide® in relation to its desired property of excluding unwanted cells and simultaneously providing a fibrous surface that improves the ability of wanted cells to grow (see claims 1 and 18 of the ‘278 patent). Finally, the ‘278 patent also teaches the advantages of making and using Bio-Gide® with chondroitin sulfate (claim 11) and glycosaminoglycan (claims 9, 12, and 24), which is also

disclosed by Chamberlain for improving his collagen tubes (pages 1395 and 1402). Given the combined teachings of the three references, it would have been *prima facie* obvious to substitute the collagen of the nerve regeneration tubes of Chamberlain with the Bio-Gide® collagen of the patents because of the known advantageous properties of the two different surfaces of Bio-Gide® in order to make and use an improved collagen nerve regeneration tube as explicitly and directly suggested by Chamberlain. Finally, because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention because the nexus between all the references makes the substitution of a known similar product (Bio-Gide® collagen for collagen type I) from a finite list of known collagens for a known similar purpose (nerve tissue healing) in order to produce a known similar result (improved tissue healing by improved interior cell growth while excluding unwanted exterior cells) with a reasonable expectation of success is also *prima facie* obvious. See *KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (U.S. 2007)*.

Applicant's arguments filed 8/5/10 have been fully considered but they are not persuasive. Applicant argues that the instant invention is distinguished from the prior art by having a soft fibrous inner surface and that subsequent research and analysis indicates that the thickness of the fibrous scar which forms along the inner surface of the tube is related to the topography of the surface (page 14 of arguments filed 10/1/09). The fact that applicant may have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be

obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In response to applicant's arguments against the references individually (i.e. Chamberlain, Geistlich '278 patent, etc., pages 14-15 of arguments filed 10/1/00), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to Applicant's argument that there is no reference to nerve regeneration or any use in connection with nerves with regards to Geistlich '278 (page 15 of arguments filed 10/1/09), first, this is an argument not in combination with the other references, and second, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the limitations of the claim. Applicant's arguments drawn to unexpected results concerning scar formation (pages 16-18 of arguments filed 10/1/09) are unpersuasive because the results are not unexpected because, as Chamberlain noted already of record, his tube can "prevent ingrowth of adjacent tissue into the gap, and thereby prevent fibrocollagenous scar formation in the gap" (pages 1399-1400 of Chamberlain). In this regard, it is again noted from the original rejection of record that the '109 patent (second Geistlich et al. reference) teaches that Bio-Gide® can be wrapped around the spinal cord and dura sheath in order to protect both from injury during spinal surgeries and also to protect the spinal area from ingrowth of connective tissue and undesired cells which might interfere with proper healing (column 1, lines 9-18 and column 1, line 54 to column 2, line 9. Also see Figures 1 and 3). Similarly, the increased number of axons seen in the instant

invention was a predictable result as indicated in the previous Office Action concerning a favorable interior environment of the tube in combination with excluding the deleterious outside environment.

Applicant argues that Integra tubes do not have a soft fibrous inner surface. This is a straw man argument because the Examiner's position is clear that the combination of the references leads the ordinary artisan to use Bio-Gide® to make the tube, not Integra. The motivation for substituting Bio-Gide® for Integra to form the tube is exactly the improved performance that results; the improved performance is not unexpected.

5. Claims 2-3, 5-6, 9-11, 19, 14-17, 22-30 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain, the '278 patent, and the '109 patent as applied to claims 2-3, 5-6, 9-11, 19, 14-16, 22-30, and 32-33 above, and further in view of Fearnot et al. (US 6,358,284, "Fearnot") for reason of record and the following. Chamberlain, the '278 patent, and the '109 patent do not teach a step of joining two opposite side edges of a collagen sheet material together to form a tube. Fearnot does teach a process for producing an implantable graft construct from a sheet of a highly purified form of an implantable tela submucosa collagen matrix (column 6, lines 45-65) formed in the shape of a tube having a seam extending longitudinally along the length of the graft wherein the seam has been sealed to resist movement of fluids from the lumen through the seam to the exterior of the tube (column 3, lines 32-38). The tubular prosthesis is envisioned for use with nervous tissue (column 2, lines 63-64). It would have been obvious to one of ordinary skill in the art at the time of the invention to make an implantable graft construct from a sheet of Bio-Gide® in the shape of a tube having a seam extending longitudinally along the length of the graft wherein the seam has been

sealed to resist movement of fluids from the lumen through the seam to the exterior of the tube because of the desire to prevent wound-derived neurotrophic factors from leaking out as suggested by Chamberlain (page 14020).

Applicant's arguments filed 8/5/10 have been fully considered but they are not persuasive because Fearnot is not needed to overcome the asserted deficiencies of the previous rejection.

6. Claims 2-3, 5-7, 9-11, 19, 14-16, and 22-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain, the '278 patent, and the '109 patent as applied to claims 2-3, 5-6, 9-11, 14-16, 19, 22-30, and 32-33 above, and further in view of Humes (US 5,429,938, already of record). Chamberlain, the '278 patent, and the '109 patent do not teach a mixture of Type I and Type IV collagen in a ratio of about 1:1 for supporting biological activity. Humes does teach the use of Type I and Type IV collagen in about 1:1 ratios to support biological activity (column 3, lines 65-66). It would have been obvious to one of ordinary skill in the art at the time of the invention to employ Humes' ratio of about 1:1 of Type I and Type IV collagen because the other references do not quantitatively teach specific ratios between Type I and Type IV collagen for the desired aim of supporting biological activity. Chamberlain provides additional motivation by teaching that collagen tubes have multiple advantages over silicone tubes, but that "the required characteristics of a nerve guide remain to be fully delineated" (page 1401). While porous collagen tubes permit diffusion of nutrients and growth-promoting factors from the external environment to the injured nerves in order to promote nerve regeneration (an observation supported by two studies according to Chamberlain), if the tube is too porous, important wound-derived neurotrophic factors may be allowed to exit the

injury site prematurely through the tube. Chamberlain reports that his own study has shown that the most favourable results were obtained with a non-porous collagen tube filled with a CG copolymer because said tube facilitated the retention of the endogenous neurotrophic factors in the nerve injury gap site while allowing for the infiltration of smaller molecular weight nutrients through the tube. Chamberlain concludes "additional experimentation with porous and non-porous collagen tubes that differ in permeability may be used to address this issue" (page 1402), which is a suggestion by the primary reference to try to optimize the ratio of Type I and Type IV collagen for the known and motivating purpose of improving the therapeutic results. The artisan would be motivated to look to the Humes reference to supply this missing information if said artisan was actually going to reduce to practice a combination of Type I and Type IV collagen because such information would be required during fabrication and use of the neural regeneration tube.

Applicant's arguments filed 8/5/10 have been fully considered but they are not persuasive because Humes is not needed to overcome the asserted deficiencies of the previous rejections and is improperly argued in isolation from the other references. In response to Applicant's argument that Humes is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Humes is in the field of cellular biology and the growth of cells, which is analogous to the other combined references.

7. No claim is allowed.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is 571-272-0883. The examiner can normally be reached on Mondays through Fridays from 0930 to 1800.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/S. G./

Examiner, Art Unit 1649

Stephen Gucker

October 1, 2010

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649